GR

ORIGINAL SUBMISSION

000001

SRA International, Inc.

1999 JUL 28 P 1:03

July 26, 1999

Dr. Linda Kahl
Office of Premarket Approval (HFS-206)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street, SW
Washington, DC 20204

Re: GRAS Notification for Transglutaminase in Meat Substitutes and Specified Dairy Products

Dear Dr. Kahl:

Two years ago, the US Department of Agriculture (USDA) in a letter (Post to Pauli, August 8, 1997) requested the opinion of the US Food and Drug Administration (FDA) regarding a claim of Generally Recognized as Safe (GRAS) for use of transglutaminase (65 ppm) in processed meats. SRA International Inc. (SRA) on behalf of our client (Ajinomoto USA) submitted this claim of GRAS, determined by scientific procedures, to the USDA. The FDA evaluated the safety evidence and responded to the USDA request stating "Based on its review, FDA has determined that, at this time, the agency would not challenge Ajinomoto's conclusion that TGP [transglutaminase] is safe under the proposed conditions of use" (letter dated January 15, 1998, Rulis to Post).

Subsequently, the FDA was notified (letter dated March 3,1998, Bernard to Kahl) that the use of transglutaminase in processed seafood at levels not to exceed 65 ppm, was exempt from statutory premarket approval requirements based on a Generally Recognized as Safe (GRAS) determination performed through scientific procedures. In response to this submission, the FDA issued a 'No Objection' letter consistent with the previously discussed Agency decision (letter dated June 22,1998, Rulis to Bernard).

On behalf of Ajinomoto USA, SRA is informing the FDA that the use of transglutaminase in Meat Substitutes and five specific categories of dairy at levels specified hereafter, is exempt from statutory premarket approval requirements based on the Generally Recognized as Safe (GRAS) determination performed through scientific procedures.

1850 M Street, N.W., Suite 290, Washington, DC 20036
Telephone: (202) 728-1400 Telefax: (202) 331-3393

The specific categories and their respective not to exceed usage levels include:

FOOD CATEGORY	USAGE LEVEL (PPM)
Processed Cheeses	250
All Natural Hard Cheeses (Domestic)	100
Cream Cheese	70
Refrigerated Yogurt	30
Frozen Desserts	20
Vegetable Protein Dishes/Vegeburgers	25
Meat Substitutes	25

A copy of the GRAS Certificate is attached as well as a summary of the data that was reviewed in support of that determination. All data reviewed in conjunction with this GRAS determination is available for FDA review at the SRA offices listed below.

If you have any questions regarding the process employed in this determination, the members of the expert panel or the underlying scientific data employed in the decision, we will be pleased to assist you.

Sincerely,

Bruce K. Bernard, Ph.D.
President

BKB/dr

ATT: GRAS Certificate
Data Summary

CC: Ajinomoto USA

SRA INTERNATIONAL, INC.
GRAS PANEL
MAY 19, 1998

A Generally Recognized as Safe (GRAS) Panel on a Transglutaminase Product (TGP) convened on May 19, 1998 at 9:00 A.M. at the offices of the Armed Forces Insitute of Pathology, Washington, DC. Panel members present were Dr. Bernard Wagner, Dr. Jay Goodman, Dr. Marcello Lotti, and Mr. Carrol Weil. One panel member, Dr. Philip Portoghese, although unable to attend the meeting, had reviewed the relevant materials and his findings were presented and discussed at the meeting. Also present was Dr. Bruce Bernard, serving as panel coordinator.

The Panel examined the materials presented in the application packet related to the TGP and considered the previous GRAS approvals for the use of TGP in processed seafood and processed meats. The intended condition of use is as a protein cross-linking agent in the following food categories and usage levels:

Food Category	Usage Level of TG (PPM)
Processed Cheeses	250
All Natural Hard Cheeses (Domestic)	100
Cream Cheese	70
Refrigerated Yogurt	30
Frozen Desserts	20
Vegetable Protein Dishes/Vegeburgers	25
Meat Substitutes	25

Based upon these data and the Panel deliberations, it was concluded that TGP is GRAS for conditions of intended use. This decision was based in part on the following:

- extensive knowledge concerning the nature of the enzyme including the fact that the active site of microbial TG is homologous to the mammalian derived enzyme
- documentation of the abundant distribution of transglutaminase in nature including the occurrence as a normal human constituent
- evidence that transglutaminase, in both the active and inactive form, has been consumed by humans since ancient times

1850 M Street, N.W., Suite 290, Washington, DC 20036
Telephone: (202) 728-1400 Telefax: (202) 331-3393

- knowledge of the producing organism; the Panel reviewed the data, agreed with the genus and species classification, and took note that there are no known pathogenic species in this genus

- previous GRAS approvals for the use of TGP in processed seafood and processed meats

- detailed evaluation of the manufacturing process

- regulatory approvals for use as an additive to human food and a history of human consumption in Japan and Europe

- an adequate package of safety studies (including exposure at high concentrations, prolonged exposure duration, and a wide variety of study types) sufficient to support the intended use in humans

- comparison of safety studies to estimations of human consumption

Transglutaminase GRAS Certificate
Expanded Use – Dairy and Meat Analog
May 1998

Panel Members

Dr. Jay Goodman

Dr. Marcello Lotti

Dr. Philip Portoghese

Dr. Bernard Wagner

Mr. Carrol W. Weil

Panel Coordinator

Dr. Bruce K. Bernard

Transglutaminase GRAS Certificate
Expanded Use – Dairy and Meat Analog
May 1998

Panel Members

_____
Dr. Jay Goodman

_____
Dr. Marcello Lotti

_____
Dr. Philip Portoghese

_____
Dr. Bernard Wagner

_____
Mr. Carrol W. Weil

Panel Coordinator

_____
Dr. Bruce K. Bernard

Transglutaminase GRAS Certificate
Expanded Use – Dairy and Meat Analog
May 1998

Panel Members

_____
Dr. Jay Goodman

_____
Dr. Marcello Lotti

_____
Dr. Philip Portoghese

_____
Dr. Bernard Wagner

_____
Mr. Carrol W. Weil

Panel Coordinator

_____
Dr. Bruce K. Bernard

Transglutaminase GRAS Certificate
Expanded Use – Dairy and Meat Analog
May 1998

Panel Members

_____
Dr. Jay Goodman

_____
Dr. Marcello Lotti

_____
Dr. Philip Portoghese

_____
Dr. Bernard Wagner

_____
Mr. Carrol W. Weil

Panel Coordinator

_____
Dr. Bruce K. Bernard

Transglutaminase GRAS Certificate
Expanded Use – Dairy and Meat Analog
May 1998

Panel Members

_____
Dr. Jay Goodman

_____
Dr. Marcello Lotti

_____
Dr. Philip Portoghese

_____
Dr. Bernard Wagner

_____
Mr. Carrol W. Weil

Panel Coordinator

_____
Dr. Bruce K. Bernard

Transglutaminase GRAS Certificate
Expanded Use – Dairy and Meat Analog
May 1998

Panel Members

Dr. Jay Goodman

Dr. Marcello Lotti

Dr. Philip Portoghese

Dr. Bernard Wagner

Mr. Carrol W. Weil

Panel Coordinator

Dr. Bruce K. Bernard

AJINOMOTO COMPANY INC.

GRAS SUMMARY/NOTIFICATION FOR THE USE OF TRANSGLUTAMINASE IN DAIRY PRODUCTS

June 1999

I. DESCRIPTION OF THE SUBSTANCE

A. COMMON OR USUAL NAME

Transglutaminase (TG) is the common or usual name given to a principal acyl-transfer catalyzing enzyme (Folk and Chung, 1973; Folk and Finlayson, 1977; Folk 1980; Folk 1982). It forms crosslinks between the γ-carboxyamide group of protein- or peptide-bound glutamine residues and the ε-amino group of lysine residues, resulting in the ε-(γ-glutamyl) lysine bonds.

B. CHEMICAL NAME

According to the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (IUBMB), transglutaminase has the following designation:

1. Formal Name
   Glutaminyl-peptide γ-glutaminyltransferase

2. Systematic Name
   Glutaminyl-peptide: amine γ-glutaminyl-transferase, EC 2.3.2.13

3. Synomyns
   There are various synonyms used for transglutaminase, whose names are based upon the organ(s) or tissue(s) of origin (e.g., Factor XIII in blood coagulating system).

C. CAS NUMBER

80146-85-6

D. EMPIRICAL FORMULA

Not applicable

000012

E. STRUCTURAL FORMULA

See prior FDA GRAS Notice #4

F. MOLECULAR WEIGHT

See prior FDA GRAS Notice #4

G. ENZYMATIC PROPERTIES

See prior FDA GRAS Notice #4

H. SPECIFICATIONS FOR FOOD GRADE MATERIALS

See prior FDA GRAS Notice #4

I. QUANTITATIVE COMPOSITION

See prior FDA GRAS Notice #4

J. MANUFACTURING

See prior FDA GRAS Notice #4

1. Source of the Enzyme

See prior FDA GRAS Notice #4

2. Manufacturing Process

See prior FDA GRAS Notice #4

II. USE OF THE SUBSTANCE

A. DATE OF FIRST USE

See prior FDA GRAS Notice #4

B. NATURAL OCCURRENCE/PAST USE IN FOODS

See prior FDA GRAS Notice #4

C. TECHNICAL EFFECT

See prior FDA GRAS Notice #4

D. INTENDED USE AND USE LEVELS

The applicant seeks to use TG in the following the food categories and at usage levels in the table below

Table 1. Food categories and usage levels

Food Category	Usage Level of TG (PPM)
Processed Cheeses	250
All Natural Hard Cheeses (Domestic)	100
Cream Cheese	70
Refrigerated Yogurt	30
Frozen Desserts	20
Vegetable Protein Dishes/ Vegeburgers/Meat substitutes	25

E. EXPOSURE

1. Calculation of Exposure Employing MRCA Data: Dairy and Meat Substitutes Only

MRCA (Chicago, IL) was retained to provide frequency distributions of intake of TG from selected dairy products and meat substitutes. The data provided by MRCA is based on the Menu Census Studies of July 1993 to June 1995 and the USDA Survey of 1987/88 for Average Grams/Eating Occasion. Assuming incorporation of TG into 100% of the food categories listed in Table 1, at the maximum approved concentration levels, consumption in the US would be as follows:

- For the total US population, the mean consumption of TG associated with these food categories would be 2.5 mg/p/day (range 1.1 – 2.9 mg/p/day).

- Of the total population (all ages), 44.8% and 0.2% are Eaters of the dairy and meat substitutes categories, respectively. The Distribution of Eaters was uniform among the age groups (approximately 44% - 51%), except ages 0-23 months (25.8%). For Eaters Only. The mean consumption for all ages was 5.5 mg/p/day. The highest consumption is in the 18 - 44 years old group (mean consumption 6.2 mg/p/day).

- The estimated consumption of TG for the 90th Percentile of Eaters Only is 10.0 and 3.0 mg/p/day, for the dairy and meat substitutes categories, respectively.

2. Total Exposure to TG

The use of TG in processed meats and seafood was declared to be Generally Recognized as Safe Under Conditions of Intended Use (GRAS) by an Expert Panel on 11 February 1997. The US Department of Agriculture (USDA) and the US Food and Drug Administration (USFDA) reviewed a notification summary that was submitted in June 1997 for processed meats. In February 1998, an approval was received from USDA. A GRAS Notification was submitted to USFDA for the use of TG in Processed Seafood on June 1997.

The calculations presented below represent total consumption of TG regardless of the source (i.e., processed meat or seafood, processed cheeses, natural hard cheeses (domestic), cream cheese, refrigerated yogurt, frozen desserts, vegetable protein dishes/vegeburgers, or meat substitutes).

MRCA (Chicago, IL) was retained to determine the total consumption of TG from a combination of all the food categories listed above.

- For the total US population, this combined category is consumed at the rate of 0.058 mg TG/p/day for all age groups, (0.044 – 0.19).
- The 90% percentile TG intake for the entire US population is 0.15 mg/p/day (0.12 – 0.55).
- Of the total US population (all ages), 55.8% are Eaters of these categories. The average consumption of TG by Eaters Only is 0.10 mg/p/day (0.79 – 0.41)

III. DETECTION OF TG IN FOOD

See prior FDA GRAS Notice #4

IV. SAFETY INFORMATION

See prior FDA GRAS Notice #4

A. *STREPTOVERTICILLIUM MOBARAENSE*

1. Classification

See prior FDA GRAS Notice #4

2. General Microbiology of the Organism

See prior FDA GRAS Notice #4

3. Genetic stability, Cultural purity and Strain Integrity

See prior FDA GRAS Notice #4

4. Non-Pathogenicity of the Organism

a) Search of the Literature for Pathogenicity

See prior FDA GRAS Notice #4

b) Pathogenicity Test of the Organism

See prior FDA GRAS Notice #4

B. TG ENZYME BROTH (following organism removal)

1. Lack of Antibiotic Production by the Organism

See prior FDA GRAS Notice #4

2. Antimicrobial Activity

See prior FDA GRAS Notice #4

3. β-Lactamase

See prior FDA GRAS Notice #4

4. Phenomycin

See prior FDA GRAS Notice #4

C. SAFETY TESTING OF THE WHOLE ENZYME PREPARATION (TG)

See prior FDA GRAS Notice #4 and toxicity summaries prepared using the JECFA method, which were provided to Dr. Linda Kahl October 30, 1997

1. Chromosomal Aberration
See prior FDA GRAS Notice #4 and toxicity summaries prepared using the JECFA method, which were provided to Dr. Linda Kahl October 30, 1997

2. Reverse Mutation
See prior FDA GRAS Notice #4 and toxicity summaries prepared using the JECFA method, which were provided to Dr. Linda Kahl October 30, 1997

3. Mouse Micronucleus
See prior FDA GRAS Notice #4 and toxicity summaries prepared using the JECFA method, which were provided to Dr. Linda Kahl October 30, 1997

4. Mouse Micronucleus
See prior FDA GRAS Notice #4 and toxicity summaries prepared using the JECFA method, which were provided to Dr. Linda Kahl October 30, 1997

5. Dermal Sensitization
See prior FDA GRAS Notice #4 and toxicity summaries prepared using the JECFA method, which were provided to Dr. Linda Kahl October 30, 1997

6. Dermal Maximization
See prior FDA GRAS Notice #4 and toxicity summaries prepared using the JECFA method, which were provided to Dr. Linda Kahl October 30, 1997

7. Allergenicity (Amino Acid Sequence)
See prior FDA GRAS Notice #4

8. Acute Toxicity
See prior FDA GRAS Notice #4 and toxicity summaries prepared using the JECFA method, which were provided to Dr. Linda Kahl October 30, 1997

9. 13-Week Toxicity
See toxicity summaries prepared using the JECFA method, which were provided to Dr. Linda Kahl October 30, 1997

10. Determination of the Presence of Aflatoxins
See prior FDA GRAS Notice #4

11. Antibiotics Evaluations
See prior FDA GRAS Notice #4

12. Antimicrobial Activity
See prior FDA GRAS Notice #4

13. Testing For Biologically Active Substances (BASs) Produced by the Genus *Streptoverticillium*

a) Literature Search:
See prior FDA GRAS Notice #4

b) Categorization of Biologically Active Substances (BASs):
See prior FDA GRAS Notice #4

c) Rationale for Selection of Hazardous Macromolecular BASs
See prior FDA GRAS Notice #4

d) Selection of the enzyme preparation
See prior FDA GRAS Notice #4

e) Trypsin Inhibitory Activity
See prior FDA GRAS Notice #4

f) β-Lactamase
See prior FDA GRAS Notice #4

g) Endotoxin
See prior FDA GRAS Notice #4

h) Phenomycin
See prior FDA GRAS Notice #4

i) Teleocidins
See prior FDA GRAS Notice #4

(1) Extraction and Mass spectrometric analysis
See prior FDA GRAS Notice #4

(2) Epstein-Barr Virus Early Antigen induction assay (EBV-EA)
See prior FDA GRAS Notice #4

SUBMISSION END

AM

SRA International, Inc.

9 November 1999

Dr. Martha Peiperl
Office of Pre-market Approval, HFS-215
FDA, 200 C Street, SW
Washington, D.C. 20204

Re: GRAS Notice (GRN #000029)

Dear Dr. Peiperl:

This letter is to provide, in writing, the results of today's telephone conversation between SRA International Inc. (Debbi Rich and myself) and the U.S. Food and Drug Administration (Dr. Michael Dinovi and you).

We reviewed Page 4, section 2 (Total Exposure to TG) given your inquiry and determined that the confusion was due to an error in the stated units. The unit in the notification was given as mg TG/p/day, where TG stands for transglutaminase and p stands for person. The correct unit is mg TG/kg/day where kg stands for kg body weight.

A consumption evaluation can, of course, be performed using calculations based upon the original units. To do so, you would use the following numbers:

- For the total U.S. population, the mean consumption is 3.4 mg/p/day (range is 1.5 – 3.9)
- For the 90% percentile of the entire U.S. population, the mean is 9.4 mg/p/day (range is 6.4 – 11.0).
- For Eaters Only (55.8% of the population) the mean consumption is 6.0 mg/p/day (range 4.4 – 6.7).

We apologize for the error, but as you stated, at least it shows you are really reading the application. It also provided an interesting brainteaser in what might have otherwise been a rather routine exercise for you.

Thank you for your assistance. We look forward to your letter of notification in the future.

Sincerely,

BKB/km

Bruce K. Bernard, Ph.D.
President

1850 M Street, N.W., Suite 290, Washington, DC 20036
Telephone: (202) 728-1400 Telefax: (202) 331-3393

000022

AM

SRA International, Inc.

FAX

To:	Martha Peiperl	**From:**	Bruce K. Bernard
Company:	FDA		
Fax:	202.418.3131	**Date:**	November 12, 1999
Phone:		**Pages:**	2
Re:	GRN000029	**CC:**	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply**

Comments

Attached is a letter from our client that indicates that Ajinomoto's transglutaminase product meets the requirements of the Food Chemical Codex, 4th Edition.

Please let me know if I can be of any further assistance.

1850 M Street, NW, Suite 290, Washington, DC 20036
Telephone: (202) 728 1400 Telefax: (202) 331-3393

AJINOMOTO U.S.A., INC.

1120 Connecticut Avenue, N.W., Suite 416, Washington, D.C. 20036

Tel: (202) 457-0284 Fax: (202) 457-0107 E-Mail: ajiws@intr.net

November 12, 1999

Dr. Bruce K. Bernard
SRA International, Inc.
1850 M Street, N.W., Suite 290
Washington, DC 20036

Dear Dr. Bernard:

This letter is a response to the inquiry of Ms. Martha Peiperl of the U.S. Food and Drug Administration's Division of Petition Control regarding the Generally Recognized As Safe (GRAS) notification (GRN 0029) of our microbial transglutaminase (TG) enzyme. This letter certifies that our microbial TG enzyme meets all of the specifications for enzymes described in the Fourth Edition of the *Food Chemicals Codex* published by the National Academy Press.

I trust this letter will suffice in addressing the inquiry of Ms. Peiperl.

Sincerely,

Robert G. Bursey, Ph.D.
Director of Scientific and Regulatory Affairs

000027

AM

SRA International, Inc.

15 December 1999

Dr. Martha Peiperl
Office of Pre-market Approval, HFS-215
FDA, 200 C Street, SW
Washington, D.C. 20204

Re: GRAS Notice (GRN #000029)

Dear Dr. Peiperl:

This letter is to provide, in writing, the supplemental information you and Dr. Linda Kahl requested in a recent telephone conversation. It is our understanding that with the submission of this information, the above-identified FDA submission is now considered complete by the Agency and that a decision will be forthcoming very shortly.

Item # 1:

Issue:
What is the 90th percentile for Eaters Only (EO) for the sum total of all food categories listed in the above identified GRAS Notice?

Response:
Consistent with the information that was provided in a telephone conversation between Drs. Kahl and Bernard, this figure is twelve 12) mg/person/day.

Item #2:

Issue:
The FDA requested a detailed description of the MRCA Survey methodology be included in our notification so that it can be made available to the public.

Response:

Background
MRCA Information Services Inc. (Palatine, IL 60067-6495) is a consulting firm that has been tracking all food preparation and consumption at-home and away-from-home through the Menu Census Surveys (MCS) since 1957. During the years of 1957 through 1977, these surveys were conducted every five years. Beginning in 1980 and continuing through the present, the surveys have been conducted continuously. The MCS studies used to obtain consumption estimates that were employed in the above-identified GRAS Notification petition were conducted during the period of July 1993 - June 1995.

1850 M Street, N.W., Suite 290, Washington, DC 20036
Telephone: (202) 728-1400 Telefax: (202) 331-3393

Methodologies Employed

Information on all foods being consumed in the U.S., with the exception of table salt, pepper, and tap water, is collected. The MCS are currently based on nationally representative, rotating samples of 500 households per 3-month period, or 2,000 households per year. Each of these samples contains approximately 5,500 individuals. The individual household reports (daily diaries) contain daily information on all food prepared and consumed during a 14 consecutive day period. The numbers of households being surveyed at any given time are uniformly distributed throughout the year. Approximately 5-6 new households are initiated into the survey each day of the year. The homemakers, who are also long-term members of MRCA's National Consumer Panel (NCP), complete the diaries. These individuals are experienced in the detailed recording of their food purchases, and reporting these purchases by mail using the dairies.

The Daily Diary

The Daily Diary provides a detail description of 1) each dish eaten, 2) items added to each dish at the table, 3) whether the meal was eaten at-home or away-from-home, and 4) which household members ate the dish. For all dishes eaten at-home, information is obtained on the number of people who ate the dish and their age(s). For homemade dishes, the reporting includes a detail description of every product used as an ingredient (e.g., fats and oils used as agents for frying, or flour for dusting breadboards). For each ingredient, the diary requires 1) the brand name of the ingredient, the physical form as obtained (e.g., liquid), the packaging material, and whether the ingredient was itself a leftover. For foods eaten away-from-home, information obtained includes specifics related to the location where the food was consumed, the name of the food service facility, and if it was eaten at the place where it was obtained.

Information on Diets, Psychographics and Household Demographics

A separate questionnaire, administered following the 14th day of reporting, provides the following detailed information for each household member: 1) detail information on the individual's age, sex, pregnancy status, weight, and height, 2) information on special diets being followed, reason for the diet, and the foods encouraged or discouraged by that diet, 3) the use of table salt, and 4) the consumption of vitamin and mineral supplements, including kind, potency, amount and frequency. In addition, an extensive set of demographic classifications is available for each household.

Intake Studies

An intake study for a given substance usually includes Frequency Distribution Reports (FDR). The FDR describes the daily intake of the substance of interest, in both milligrams (mg/day) and milligrams per kilogram of body weight (mg/kg/day), across a series of age groups. The data is expresses for two different types of groups, those individuals that consume a particular food type (Eaters Only) and all individuals whether they consume the food type or not (All).

The intake study for a given substance is based on a detailed listing of all the foods that are known to contain the substance and includes information obtained from manufacturers. The amount of the substance consumed by eating any food item on the list is computed by multiplying the concentration of the substance in that food by the quantity of the food eaten (see below).

Quantities of Food Eaten

The daily reports detailed above provide incidence information (i.e. the frequency of consumption of each food type by each individual). Information on the quantity of food consumed per eating occasion is available from data obtained and published by the USDA in the National Food Consumption Survey (NFCS, 1977-78). The NFCS reports quantities of food consumed (per eating occasion) based upon various demographic variables (e.g., age, sex).

Since the USDA Survey provides grams of foods for end dishes as-eaten, these estimated average amounts per eating occasion are used only to quantify dishes as-eaten, such as milk when consumed as a beverage, or sugar when added to coffee or tea, or oil used as a salad dressing. When the products are used at-home as ingredients or frying agents, in preparing other foods, the amounts consumed are computed as percentages of the corresponding amounts of the end dishes in which they were used. These percentages are based on estimates obtained from standard recipes.

Intake Amounts

Based upon the above, the quantity of the substance consumed at a single eating occasion is calculated by multiplying the average grams per eating occasion by the concentration of the substance. These calculations are segregated by food category and age.

The estimated consumption of each food type at each eating occasion is summed for each food type for each individual for each day and the total 14-day consumption period. Corresponding sub-totals are accumulated for the intake of the substance from each food sub-category, and from the total diet, separately for each person, and for each day, treating each day for each person as an independent observation. These calculations are employed to provide consumption estimates on a daily individual person (Person-Day) basis. These daily consumption figures for each individual are also summed over the 14-day period to provide estimates on a 14-Day Average Daily Basis.

Intake Study Report

The above methodologies generate data that can be are provided in Intake Study Reports. These reports provide detailed analyses of the frequency distributions of the average daily intake of the substance by age groups (in five percentile increments), for the Eaters Only and separately, for the total sample of eaters plus non-eaters. The shape of the distribution is obtained from the average daily consumption at a variety of percentiles (e.g., 50^{th}, 90^{th} 95^{th} and 99^{th} percentile). This information can be obtained as mg/day or mg/kg/day for individual food sub-categories, cumulative food groups; and all foods combined.

From a conceptual point of view, it is important to understand that the mean intakes by eaters plus non-eaters (Total Sample) for non-overlapping foods are additive for the Total Sample (eaters plus non-eaters) but they are not additive for Eaters Only. Total Sample means are additive because the specific individuals and (therefore the sample size) employed to determine the mean (denominator) are the same for each mean. The numerators consist of the amounts of the food substance that the person consumes on either a given day or during all 14 days of the survey. The mean intakes of non-overlapping foods by Eaters Only are not additive since the specific individuals eating one food source may not be the same as those consuming another food type. Some eaters may eat foods in category A, but not category B, while others may consume foods from both categories, or only from category B. It is possible to compute the mean of eaters only of two combined food sources, provided one knows the net, unduplicated eaters of the combined food source and the number and mean eaters of each source alone.

We trust that the information provided answers the last two issues raised by FDA. We thank you in advance for providing, in the very near future, an Agency response to our GRAS Notification.

Sincerely,

Bruce K. Bernard, Ph.D.
President

CC: L. Kahl (FDA)